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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,424	05/09/2001	Christopher R. Tudan	SMAR014	5001

24353 7590 10/20/2003

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	18

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,424	TUDAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5 and 10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9, 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is a response to the "Amendment and Response" filed 17 July 2003 (Paper No. 15) in reply to the Non-Final Office Action mailed 20 March 2003 (Paper No. 14). Claims 5 and 10-20 were withdrawn from consideration and claims 1-4, 6-9, 21 and 22 were considered in Paper No. 14. Claims 1, 3, 4, 9 and 21 were amended and claim 22 was canceled in Paper No. 15. Claims 1-21 are pending and claims 1-4, 6-9 and 21 are under consideration.

Election/Restrictions

Applicant's request for rejoinder of claims 5 and 10-20 is acknowledged. As indicated in the original restriction requirement, the restriction requirement among the linked inventions is subject to the nonallowance of the linking claim, claim 1. Upon the allowance of the linking claim, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claim will be entitled to examination in the instant application.

Priority

Receipt of the foreign priority document and Declarations signed by inventors Merzouk and Salari clearly indicating the foreign priority claim is acknowledged. Applicant's assurance that Declarations signed by the remaining inventors will be forwarded when they become available is also acknowledged. The claims will be afforded priority to the foreign application as soon as the claim is perfected by the submission of a Declaration signed by inventors Tudan, Arab, Saxena, Eaves, Cashman and Clark-Lewis.

Claim Objections

Objection to claim 9 is withdrawn. Applicant's right to reintroduce the deleted subject matter upon notification of an allowable linking claim is acknowledged.

Response to Amendment

Rejection of claim 22 is rendered moot by cancellation of the claim.

Claim Rejections - 35 USC § 112

Claims 1-4, 6-8 and 21 stand rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for reasons of record and herein below in the response to arguments. Please note, although the written description rejection was not previously applied to claim 21, the claim is clearly directed to a method of using the CXCR4 antagonists having the same scope as the CXCR4 antagonists of claims 1-4 and 6-8 and therefore lacking adequate written description for the same reasons set forth regarding claims 1-4 and 6-8.

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting the rate of BFU-E or CFU-GM multiplication, does not reasonably provide enablement for a method of promoting proliferation of all hematopoietic cells for reasons of record and herein below in the response to arguments.

Rejection of claim 4 under 35 U.S.C. 112, first paragraph, as lacking enablement is withdrawn in view of the limitation of the claim such that the nucleic acid sequence is limited to encoding SDF-1[P2G] (SEQ ID NO:1) or a fragment or analog thereof.

Rejection of claim 21 under 35 U.S.C. 112, second paragraph, as indefinite is withdrawn.

Response to Arguments

Claims 1-4, 6-8 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the rejection of record, the claims have been amended such that the CXCR4 antagonist is limited to comprising SDF-1[P2G](SEQ ID NO: 1) or a fragment or analog thereof. Applicant argues that the claimed subject matter is fully described because the specification exhaustively describes and reduces to practice a large number of species representing the claimed genus of CXCR4 antagonists comprising SDF-1[P2G](SEQ ID NO: 1) or a fragment or analog thereof. Specifically, Applicant identifies fragments of SDF-1[P2G] having fewer than 9 amino acids and sequences having substitutions at positions 5, 6, 7 or 8 of SDF1[P2G]. Further, Applicant argues that the specification discloses relevant identifying characteristics of molecules corresponding to the claimed genus, such as, the ability to bind CXCR4 and exhibit CXCR4 antagonist activity.

These arguments have been fully considered but are not found persuasive because, although the specification provides adequate descriptive support for fragments of SDF-1[P2G], the disclosure does not adequately describe analogs of SDF-1[P2G]. Although the term "analog" connotes some degree of structural similarity, the structural limitations of an SDF-1[P2G] analog are not defined in the specification. As the structural metes and bounds of an SDF-1[P2G] analog are unclear, the limitation is interpreted to encompass any CXCR4 antagonist having even a very low degree of structural similarity to SDF-1[P2G]. Thus, the SDF-1[P2G] analog of the claims still encompasses molecules defined solely by their principal biological property with no disclosure of structure. It is acknowledged that the specification describes CXCR4 antagonists comprising some limited modification of the SDF-1[P2G] sequence and inclusion of a proline-amino acid chimera or Bicyclic Turned Dipeptide at some positions; however, the species provided do not adequately represent the full scope of SDF-1[P2G] analogs because the specification does not limit analogs to comprising amino acid substitutions or even to comprising amino acids at all. Therefore, for reasons of record and herein above, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Claims 1-4 and 6-9 were rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claims because the specification, while being enabling for a method of promoting the rate of BFU-E or CFU-GM multiplication, does not reasonably provide enablement for a method of promoting proliferation of all hematopoietic cells for reasons of record and herein below in the response to arguments. In response, Applicant contends that specification teaches promoting the rate of hematopoietic cell multiplication and increasing the

circulation of hematopoietic cells by CXCR4 antagonists using different hematopoietic cells, and cites pages 49-52 of the specification to support this contention.

The experiments described on pages 49-52 are addressed in the previous Office Action:

> The instant disclosure teaches an increase in the number of cycling BFU-E and CFU-GM cells in response to CXCR4 antagonists (Example 2) and enhanced proliferation of these same cell types in an *in vivo* engraftment model (Example 3; Figure 2). However, the specification also teaches that the antagonists had no effect on the cycling status of long-term culture initiating cells (Figure 2). Therefore, although the it appears that the disclosure provides adequate guidance to obtain a proliferative response from BFU-E and CFU-GM cells there are clearly examples of cells within the genus of hematopoietic cells that would not proliferate when treated according to the claimed method. (page 8)

Thus, the specification teaches that the method is enabled for promoting multiplication of two types of hematopoietic cells and not enabled for others.

Applicant argues that the data in Figure 2 "is merely an embodiment of an alternative aspect of the invention, representing as it does a single experiment of an alternative aspect of the invention" and "does not provide a basis for either an assertion that the methods of the invention will not work in connection with long-term culture initiating cells in particular or hematopoietic cells, other than BFU-E or CFU-GM cells, in general" (page 9). With regard to the data presented for long-term culture initiating cells being merely an embodiment of an alternative aspect, it is not clear how this undermines the Examiner's position because the data still indicate that some hematopoietic cells do not proliferate in response to the CXCR4 antagonists. Thus, the data demonstrate that the methods disclosed in the application as effective in stimulating BFU-E or CFU-GM cell proliferation cannot be directly extended to a method of stimulating proliferation of all hematopoietic cells. It is also unclear why Applicant claims that the data presented do not provide a basis for asserting that the methods of the invention will not work for

long-term culture initiating cells when that appears to be what the data indicate. However, it should be kept in mind that the Examiner's position is not that the method will not work, but that it would require undue experimentation to enable the full scope of the claimed invention. The data presented in Figure 2 at least demonstrate that stimulating proliferation of long-term culture initiating cells would require additional method steps not disclosed in the instant application. Therefore, to practice the claimed invention, the skilled artisan would have to engage in undue empirical experimentation to develop the claimed method such that it could be practiced according to its full scope.

With regard to the teachings of Hodohara *et al.*, Applicant urges that the teachings therein simply document the results of experiments conducted using a combination of native SDF-1 and TPO and merely notes a lack of response in the experiments where SDF-1 alone was used. For this reason, Applicant argues that Hodohara's teachings cannot be considered an indicator of the state of the art, or be used to draw conclusions regarding efficacy or enablement of the instant invention because Hodohara does not teach or disclose effects of a CXCR4 antagonist. This argument is not found persuasive because Hodohara *et al.* discloses the effect of SDF-1, *acting through the CXCR4 receptor*, stimulates proliferation of megakaryocytes when coadministered with thrombopoietin. Furthermore, Hodohara *et al.* does indeed disclose that the CXCR4 antagonist T22 inhibits the effect of SDF-1 on thrombopoietin-stimulated proliferation (see especially Table 2 and Table 6). These data clearly demonstrate the effects of a CXCR4 antagonist on a hematopoietic cell that is the opposite of what is shown for BFU-E or CFU-GM in the instant application. Thus, the teachings of Hodohara *et al.*, like the data presented in Figure 2, indicate that general enablement for stimulating any hematopoietic cell to proliferate using a

CXCR4 antagonist cannot be predicted based on a demonstration of enablement for BFU-E and CFU-GM cells. In fact, the skilled artisan would have to engage in undue experimentation to practice the claimed method of stimulating proliferation of, at least, megakaryocytes and long-term culture initiating cells.

Applicant's arguments have been fully considered but are not found persuasive either individually or as a whole; therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-8 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "analog" in claims 1, 3 and 21. The metes and bounds of the limitation are not explicitly set forth in the specification and, although as a term of art "analog" connotes some structural limitation, the degree to which a compound can differ from the reference compound and still meet the limitation is unclear. Therefore, it is not possible to ascertain the scope of the SDF-1[P2G] analog of the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

JAMES KETTER
PRIMARY EXAMINER